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Dockets Management Branch
Food and Drug Administration, HFA-305
5630 Fishers Lane, Room 1061
Rockville, MD 20857

Re: Docket No. 00D-1336; Draft Guidance for Industry: Pediatric Oncology Studies in Response to a Written Request, 65 Federal Register 38564 (June 21, 2000)

Dear Sir or Madam:

Bristol-Myers Squibb is a diversified worldwide health and personal care company with principal businesses in pharmaceuticals, consumer medicines, beauty care, nutritionals and medical devices. We are a leading company in the development of innovative therapies for cardiovascular, metabolic, oncology, infectious diseases, and neurological disorders.

The Bristol-Myers Squibb Pharmaceutical Research Institute (PRI) is a global research and development organization that employs more than 4,300 scientists worldwide. PRI scientists are dedicated to discovering and developing best in class, innovative, therapeutic and preventive agents, with a focus on ten therapeutic areas of significant medical need. Currently, the PRI pipeline comprises more than 50 compounds under active development. In 1999, pharmaceutical research and development spending at PRI totaled $1.4 billion. Bristol-Myers Squibb actively participates in the pediatric research programs and, to date, has requested Written Requests for Pediatric Studies for 17 drugs. Based upon this extensive and ongoing experience with the program, and in consideration of our longstanding leadership role in the development of oncology drug products, we are very interested in and well qualified to comment on the subject FDA draft guidance on pediatric oncology studies.

BMS supports the Agency's initiative to generate new knowledge to assist practitioners in the care of children with cancer and help provide pediatric patients early access to emerging new drugs. We believe there is also value in providing pediatric patients with access to emerging new uses of approved drugs. The draft *Guidance for Industry on Pediatric Oncology Studies In Response to a Written Request* (the "Guidance") is an

excellent first step towards working with the pharmaceutical industry to achieve these goals. We do, however, have several comments on the Guidance that we believe would clarify the process for receiving and complying with written requests.

Sections III and IV

The Agency has correctly noted that the study of oncology drugs in children merits special consideration and we believe it is worth restating three particular issues: 1) many pediatric patients suffer from different tumors than those found in adult patients, 2) known and potential differences in the biology of pediatric and adult tumors make it difficult to extrapolate clinical drug effects from adults to children, and 3) pediatric populations are complex, heterogeneous and small in numbers. As a general matter, we agree that flexibility is needed in structuring pediatric studies and that the written requests for oncology drugs should reflect the complexities of studying drug effects in pediatric populations.

The draft Guidance recognizes that the FDA may apply "flexible regulatory approaches" in the approval process for oncology drugs to treat pediatric patients. We commend the FDA on this approach and believe it is warranted because of the complexities of studying drugs in pediatric populations. Given the relatively small size of most oncology pediatric patient populations and the paucity of approved therapies to treat children with cancer, an Agency requirement of extensive studies to support Written Requests would be impractical and counterproductive with regard to the achieving the goals reflected in Section 111 of the Food and Drug Administration Modernization Actof 1997 ("FDAMA"). We would like FDA to clarify that the "regulatory flexibility" will be applied to both new agents and drugs which are already commercially available, drugs which, in some instances, clearly have utility against pediatric malignancies.

Dr. Pazdur's letter of February 14, 2000, on the development of 'new agents' for use against pediatric malignancies clearly reflected the Division's focus away from already marketed drug products to unapproved compounds. The draft Guidance follows this direction. Both provide brief guidance on pediatric development within overall clinical development programs, including the need for both Phase I and Phase II pediatric study data. Dr. Pazdur's letter and the Agency's draft Guidance do not acknowledge that typically a new oncology drug cannot be introduced into pediatric patients until some adult clinical data have been generated. It is important that this FDA focus on 'new agents' and the attendant timelines for generating what would apparently be considered to constitute 'adequatc' pediatric data is fundamentally inconsistent with the existing, time-limited (by sunset) pediatric incentive provisions. For this reason (and in recognition of the overwhelming success of the pediatric incentive provision outside of the oncology therapeutics arena), it is clear that these provisions should be made permanent.

Both FDA and the industry have struggled with the implementation of the FDAMA pediatric research provisions for approved oncology drugs; this is evidenced by the relatively low number of oncology drug written requests which have been issued to date.

Further witness to this struggle has been the inability of FDA to issue a specific guidance on the "information on health benefits" requirement for marketed oncology drugs. Clearly, such specific guidance has been confounded by the fact that even Phase II oncology trials have evolved 'standards of care' in pediatric oncology, that many drugs which have been marketed for a number of years have already been incorporated into combination regimens within those trials and that such combination regimens have been accepted as treatment standards. However, despite these confounding factors it is appropriate and consistent with the intent of the pediatric provisions that FDA provide guidance concerning studies with marketed drugs which could generate acceptable 'information on health benefits', (and that such guidance take into consideration the difficulty of conducting timely pediatric oncology Phase III studies). The subject guidance document should also be expanded to address what might represent acceptable yet flexible approaches for dealing with the regulatory requirement for the assessment of 'contribution' of drugs after they have already been accepted within the pediatric oncology community as a component of 'standard' combination therapy.

Paragraph 1 of Section III notes that surrogate markers likely to predict clinical benefit might be appropriate as a basis for approval. In some adult malignancies tumor response has not been accepted as a valid surrogate for clinical benefit, (e.g. nsclc). Are there certain pediatric tumor types or stages of disease where the FDA might find the use of surrogate markers inappropriate? Guidance on this matter is requested.

Section IV provides guidance on the scope and content of the written requests that the Agency might issue pursuant to Section 111 of FDAMA. Section IV does not, however, consider fully the dynamics of studying drugs in different pediatric age groups. We would like clarification on FDA's expectations on this issue. In particular, metabolism of drugs undergoes dynamic changes through the maturation and growth of children, and important determinants of drug disposition such as body composition, renal function, P450 metabolic mechanisms, and conjugation, and susceptibility to adverse events may vary in different age groups in the pediatric population (6 mo-2 years; 2 – 6 years; 6-12 years; 12-16 years). There are valid scientific reasons for studying drug pharmacology separately in each of these age groups, and this approach has been requested by the Agency in other therapeutic areas (e.g., anti-infectives). The patient numbers available for pediatric oncology studies make separate age-group studies not feasible. We believe the Agency's guidance on this issue would be instructive and helpful in structuring pediatric studies.

We believe some guidance on the study of supportive care products in pediatric populations would be beneficial.

Section V

There are several items in Section V of the Guidance that we believe could benefit from clarification:

- Often pediatric patient populations included in Phase II/III studies are significantly more heterogeneous than adult populations in Phase II/III studies. We would like the

Agency to clarify the degree of heterogeneity that might be acceptable in pediatric studies.

- Please clarify whether the term 'cooperative group' as it is used in the context of this Guidance refers to solely U.S. cooperative groups or to cooperative groups world wide.
- It would be helpful if the guidance could outline how the Agency will categorize requests for consultations on pediatric protocols (i.e. Would these be considered 'special protocols', thus qualifying for a Type A meeting to be scheduled with 30 days of the request?)
- Section V would benefit from some expansion to address the generation of Phase I combination data prior to the initiation of Phase II combination studies.
- The suggestion that 'patient benefit' of an investigational product might be demonstrated by "add-on" designs in Phase II or 'pilot' studies (Section V2., page 4-5) appears inconsistent with past Agency perspectives. In most cases the Agency has required data from Phase III trials to support a conclusion of 'contribution' to efficacy when new drugs are 'added' to established therapies. Furthermore, the draft Guidance states "information from phase 3 studies would generally not be included in a Written Request". We would like the Agency to provide more specific guidance on the type of studies which could generate adequate information to support a conclusion of 'contribution' to combination therapy.

Section VI

We suggest that Section VI be expanded to clarify that it is the sponsor's option to submit reports of studies covered in a Written Request without first requesting 'advice' from FDA.

BMS appreciates the opportunity to provide comment and respectfully requests that FDA give consideration to our recommendations. We would be pleased to provide additional pertinent information as may be requested.

Sincerely,

Laurie Smaldone

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